ADENOMATOID TUMORS OF THE GENITAL TRACT *

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Fifteen cases of a tumor with definite anatomic features, limited to the epididymis, testicular tunics and the serosal surface of the uterine tube, have come to our attention in the past 2 years. A survey of the literature makes it probable that the same tumor has been seen and described by others under a variety of names (see "Discussion" below). Hinman and Gibson 1 (1924), Thompson 2 (1936) and Scalfi 3 (1936), in their reviews of the literature on tumors of the epididymis, spermatic cord and testicular tunics, agree that reported tumors of these sites are uncommon, and that those of the epididymis are exceedingly rare. However, in the past several years isolated case reports and reports of small series of cases have appeared in which the clinical and gross findings, the microscopic reports, and photomicrographs appear to be identical to those of the tumors to be described. Inasmuch as the reported series is still small, even in the aggregate, we believe it important to report our findings in this group of 15 cases, the largest series studied to date.

CLINICAL AND PATHOLOGIC ASPECTS

In Table I there are summarized the salient features of the reported clinical findings and the topographic anatomy, and in Table II, the notable pathologic features of this tumor group.

From a consideration of the data contained in the tables the following condensation of the clinical details is possible: All but 2 of the tumors were present in males ranging from 20 to 68 years of age. Most patients were in the third and fourth decades of life. In only 1 of the 2 cases in females could the age be ascertained and in that instance it was 67 years. The tumor was discovered on routine physical examination, or as an incidental post-mortem finding or surgical finding. presumably without previous symptoms in 6 cases; and was associated with pain or tenderness, either with or without exertion, at the local site in 8 instances. Progressive increase in size was noted in 5 cases. usually on the basis of the patient's own testimony. A history of trauma was part of the clinical record in only 2 cases. In those instances where the tumor was discovered only incidentally, on either recorded physical examination or at operation for some other complaint, or at the autopsy table, there was, of course, no way of knowing how long it had been present; but when the patient did know of the tumor's presence, the shortest reported period prior to operation

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TABLE I
Clinical Data on 15 Cases of Adenomatoid Tumors of the Genital Tract

Location, topographic anatomy and source	Lower pole of the epididymis. Sharply demarcated nodule 1.5 cm. in diameter.	Adherent to the tunica vaginalis, exact site not specified.	In the "epididymis, independent of the testicle."	"Supernumerary body on the left testicle."	Upper pole of testicle.	Lower pole of epididymis.
History, symptoms and signs	Discovered on routine physical examination. No symptoms noted.	Patient discovered a pea-sized, freely movable nodule in the region of the rt. testicle. There was pain locally on exertion. In 6 mos. there was a progressive increase in size up to 2 cm. in diameter.	History of blow to rt. testicle 10 yrs. before operation. Five yrs. later a small pea-sized swelling was noted which grew slowly in the last 1½ yrs. Another injury caused increase of mass to goose-egg-size with subsidence in 3 wks. Recent rapid growth to 2.5 cm.	Incidental finding in varicocele operation.	Small growth in upper pole of left testicle with pain, of 3 yrs.' duration, with no increase in size. Onset attributed to blow to region.	Patient noted swelling, 10 yrs. prior to operation, in region of 1t. testicle, with subsequent, slight, gradual increase in size. Complaints of regional tenderness after long standing or walking. A pea-sized nodule present for 5 yrs. prior to operation.
Race	W	Μ	м	M	W	А
Age	29	23 ,	28	32	36	44
Sex	M	M	М	M	M	M
A.M.M. Accession*	97945	94094	84615	81346	84648	76268

Clinical Data on 13 Cases of Adenomatoid Tumors of the Genital Tract TABLE I (Continued)

A.M.M. Accession	Sex	νβγ	Race	History, symptoms and signs	Location, topographic anatomy and source
97904	×	16	М	Tumor of rt. testicle present for "some Itime." Tender to pressure and painful on sudden movement.	Lower pole of epididymis.
94348	×	90	M	Painful tumor in left side of scrotum of 8 Imps.' duration, with threefold increase of size during that time.	Lower pole of epididymis. Shelled out easily at operation.
91983 A-36-1427†	Ħ	49	M	Incidental autopsy finding.	Uterine tube.
S-13031‡	Ē	۸.	၁	Incidental finding at operation.	"Encapsulated tumor on fallopian tube."
S-692‡	M	33	M	Duration and symptoms unknown.	Mass about the size of a bean was dissected away from the region of the rt. testicle.
S-15463‡	M	34	W?	Mass in region of testicle, known to be present for 3 yrs. prior to operation.	Tumor on the surface of the tunica vaginalis over the lower pole of the testis.
A-2633‡	M	89	ပ	Incidental autopsy finding.	Lower pole, it. epididymis.
100648	M	22	ပ	Patient noted a small, tender nodule at the upper pole, it. testicle, a wks. prior to operative removal. No history of trauma or infection.	Tumor nodule involving only the "capsule" of the upper pole of the lt. testicle.
101680	×	38	Α	Nodule present in scrotum for g yrs., with very gradual increase in size during that time. Painful "at times."	Nodule in the globus minor of the epididymis.

* All cases except those noted below are from the Army Institute of Pathology, Army Medical Museum, and represent cases submitted through U. S. Army Medical Department sources. All cases have been incorporated in The General Tumor Registry, a subdivision of The American Registry of Pathology, The National Research Council, housed at the Army Medical Museum.
† Contributed by Dr. A. A. Nelson, Washington, D.C., from the Autopsy Series, University of Minnesota, School of Medicine, Department of Pathology, ‡ Contributed by The Division of Pathology, The National Institute of Health, Bethesda, Md.

TABLE II
Gross and Microscopical Observations on 15 Adenomatoid Tumors of the Genital Tract

Notes	in Serologic nd tests for ga-syphilis, and in-routine blood		aal- aal: ced	ss.		No recurrence or metastasis 4½ yrs. after operation. Aschheim-Zondek test negative prior to operative removal.
Special stains	Fat stains (sudan IV in isopropyl alcohol) and mucicarmine stains negative in all cases for stain.	able material in the vac- uoles or gland lumina. Best's carmine method for glycogen stained neg- atively in all cases, using formaldehyde-fixed fissue,	prepared from formal- prepared from formal- dehyde-fixed tissue as the only source material. Reticulum stains showed a well defined perifollicu-	Phosphotungstic acid hematoxylin stains showed well defined cell borders without processes in the lining cells of the gland-like groups.	nuscle bundles in some of the sections was confirmed by Masson's trichrome stain.	
Microscopic morphology	Mixed gland types. Mainly microfollicular, partly macrofollicular, and scanty, solid, cord-like formations. Fibrous stroma.	Mainly macrofollicular. Stromal back-ground is dense, fibrous.	Mixed gland types: microfollicular, macrofollicular, and solid cord-like formations Small lymphocytic nodules present in the periphery. Fibrous stroma.	Macrofollicular type predominantly. Diffuse, light, lymphocytic infiltration in a predominantly fibrous stroma.	Mainly of the solid cord-like type, with occasional microfollicular formations. Stroma dense, fibrous.	Macrofollicular type predominantly. Stroma loose and fibrous.
Gross morphology	Circumscribed, white firm tumor mass 1.5 cm. in diameter.	Dumbbell-shaped nodule 2.6 X 1.3 X 0.8 cm. in size. A thin capsule invested the whole. The cut surface was smooth, homogenous, translucent, and bulged slightly.	Encapsulated, globular, firm, elastic nodule, 2.5 cm. in diameter. The cut surface was grayish pink with irregular coarse areas of grayish white, and the whole had a whorled, fibrous appearance.	Portion of resected epididymis which overlay and partially enveloped a firm, gray, roughly spherical nodule within it, measuring 1.2 cm. in diameter. The mass appeared circumscribed and probably encapsulated.	Resected testicle, epididymis, and spermatic cord. An irregular, apparently circumscribed nodule was present, lying between the head of the epididymis and the base of the spermatic cord, without any evidence of invading regional tissues.	The resected tail of the epididymis was found to be indurated. Cut section revealed a spherical, hard nodule 1.2×1.0 cm., which did not appear to be encapsulated. The cut surface was white and glassy, with faint yellow flecking.
A.M.M. Accession	97945	94094	84615	81346	84648	76268

TABLE II (Continued) Gross and Microscopical Observations on 13 Adenomatoid Tumors of the Genital Tract

A.M.M. Accession	Gross morphology	Microscopic morphology	Special stains	Notes
97904	Poorly circumscribed nodule of firm, white, neoplastic tissue, measuring 1.0 cm. in greatest diameter, which encroached on regional testicular tissue without evidence of invasion.	Mainly microfollicular. Slight diffuse lymphocytic infiltration in the fibrous stroms, and an occasional small lymphocytic interstitial nodule.		
94348	Encapsulated, smooth gray-white nodule measuring 1.5 X 1.2 cm. Cut surface white, firm, tough.	Mainly microfollicular. Dense collagenous stroma. Large bundles of smooth muscle present in the periphery. Occasional interstitial lymphocytic nodule present.		,
91983, A-36-1427	None available. Reconstruction from microscopic picture is that of a nodule extending from the serosa through the thickness of the tubal wall.	Mainly macrofollicular. Fibrous stroma.		
S-13031	"Encapsulated tumor in fallopian tube."	Mainly macrofollicular. Fibrous stroms.		
S-692	Mass about size of a bean dissected from region of "rt. testicle." (Microscopic section shows it to be epididymal.)	Microfollicular and solid cord-like types. Fibrous stroms.		
S-15463	Tumor nodule appearing as a part of the tunica vaginalis. The cut surface was "fibroid in character."	Mainly macrofollicular. Stroms partially fibrous with bundles of smooth muscle chiefly in the periphery. A few small clusters of lymphocytes and a slight diffuse spread of them are present interstitially.		
A-2633	Circumscribed, dense yellowish mass in the inferior pole of the epididymis, which is "walled off."	Mainly macrofollicular, and to a lesser degree microfollicular. Mainly fibrous background. Small number of smooth muscle bundles in the periphery.		
100648	Oval mass of pinkish gray tissue o.5 cm. in diameter in "capsule" of testicle. Cut surface shows gray, faintly nodular, glistening, resilient tissue.	Mainly solid cord type. Partially encapsulated. Diffuse, slight, round-cell infitration interstitially.		
101680	Globus minor of the epididymis received in which there was a firm, hard nodule, 1.0 cm. in dismeter, which was partially encapsulated.	Mainly macrofollicular. Number of smooth muscle bundles chiefly in the periphery of the tumor. Numerous interstitial lymphocytic nodules. Moderate diffuse lymphocytic interstitial infiltrate.		

was 2 weeks and the longest 10 years. The size estimated by the surgeon or medical examiner was usually larger than the recorded gross dimensions as determined by the pathologist. The clinical appreciation of size probably took into consideration more than the tumor proper, possibly enlargement of the regional tissues consequent to blood and lymph stasis.

The following appears to be a reasonable composite gross description of this tumor group: The growths tend to be small, the largest in this series measuring 3 by 2 by 1 cm., the smallest, 0.5 cm. As a rule the tumor is globular, circumscribed and firm even to the point of induration. On section the cut surface varies from white to yellowish or pink and is glistening and may show either a smooth or finely fibrous stroma. (In one instance it was reported as being finely nodular.)

In our series the tumor was found either in the epididymis, the tunics of the testicle, or the serosal surface of the uterine tube. For tumors (2) from the last situation the gross descriptions are not available, but the microscopic sections show a neoplastic involvement, apparently growing into the underlying muscle coats from a superficial origin. In no instance was there any evidence, surgical or pathologic, of invasion of regional tissues or of metastases.

The microscopic anatomy of the tumors showed considerable variation. All of the tumors had a fibrous stroma varying from a loose collagenous meshwork to a dense, and in some instances, partially hyalinized fibrous stroma. Between the bundles of connective tissue, glandlike spaces were so distributed that fibrous stroma was present between all of them. Whatever the form of these glandular spaces their course lay in many directions, even in a single microscopic field. The glandular structures were of variable pattern, but the cell type was fairly characteristic. Some of the tumors tended to show a preponderance of one gland-like type over the other, but the rule was to find a variable picture, particularly in multiple sections. The variation in the glandlike structures was from almost solid cords (Fig. 2) of cuboidal and low-columnar cells to greatly dilated spaces lined by markedly flattened cells (Fig. 4). In Table II these are called "solid cord-like," "microfollicular" and "macrofollicular," respectively. In all of the tumors, examples of all types were seen. The majority of the cells contained vacuoles of variable size (Fig. 5), reaching exceedingly large proportions (Fig. 8), and producing a signet-ring appearance (Fig. 6). The vacuoles were always sharply demarcated. The nonvacuolated cells, best seen where the tumor formed cords, varied from cuboidal to low-columnar, had a finely granular, acidophilic cytoplasm, and a round or oval, centrally placed nucleus rich in chromatin. Cilia were

absent. No pigment was present in any of the cells. In many instances markedly vacuolated cells could be seen with only thin cytoplasmic strands connecting them (Fig. 6). In other places, gland-like spaces were lined by cells with shreds of cytoplasm still present along the free border (Fig. 7), suggesting gland formation by fusion of vacuoles. The gland lumina contained no material staining with hematoxylin and eosin, such as is seen in lymphangiomas. No blood cells of any kind were found within the lumina. This cell type is common to all of these tumors, as is also the pattern produced by these cells. This pattern is consequently considered the primary unit of structure for this tumor.

It was previously noted that the composition of the stroma was variable. Occasionally, bundles of smooth muscle were present in considerable quantity (Fig. 11). In none of these instances was the microscopic evidence convincing that the muscle was an integral part of the tumor. It appeared more reasonable to assume that the smooth muscle represented inclusion of pre-existing muscle in an expansile tumor growth.

An attempt was made to determine the nature of the vacuoles. Special stains for lipids were negative in all instances. The mucicarmine stain revealed neither mucinous granules nor mucin vacuoles in any of the sections. None of the material available for study had been preserved in ethyl alcohol. Therefore our attempts at staining these vacuoles with Best's carmine method for glycogen made use of formaldehyde-fixed wet tissue and/or the paraffin blocks prepared from formaldehyde-fixed tissue. The results were uniformly negative. The question, therefore, of the glycogen content of these vacuoles must remain open. The phosphotungstic acid hematoxylin stain revealed no fibrillar processes in any of the cells, even when they were present in solid cords, or when they lay in small clusters in the interstitial tissues. On the contrary, this stain revealed that the cell borders were well defined, smooth, and free of either brush borders or cilia. Reticulum stains showed a characteristic pattern of the reticulum meshwork (Fig. 10) rather intimately applied to the gland-like spaces in strands from one to three rows thick. There was no evidence of a basement membrane. The interstitial tissue contained a scattering of lymphocytes, with an occasionally admixed monocyte (Fig. 3). Plasma cells, eosinophils and neutrophils were absent. Occasionally, a cluster of lymphocytes produced a small nodule without a secondary center. Other portions of the same tumor, or other tumors, were without round cell infiltration. There was no evidence of the effects of chronic inflammation, such as scarring, adjacent to the lymphocytic foci. In none

of the sections studied was there any evidence of invasion of the regional tissues. Microscopically, the tumors could be shown to be either sharply circumscribed or encapsulated (Fig. 1). In most instances there was no marked compression of the regional tissues, suggesting that the rate of tumor growth was slow.

DISCUSSION

Inasmuch as this tumor appears to be confined to the genital tract, origin from misplaced embryonic or fetal genital ridge is a tempting hypothesis. Accordingly, a number of testes and epididymides, with their adjacent tissues, from stillborn infants, and similar anatomic structures from fetuses, were subjected to frozen section study from slices made at close intervals. No structures resembling these tumors were encountered. There are no reports of cellular elements in the development of the embryonic genital ridge which resemble those of the tumor described above. It is conceivable that, since these tumors may arise from an abnormal group of genital ridge cells, the method of sampling employed is inadequate. One should examine a very large number of specimens before accepting or dropping such a postulate as to origin. The question of the tumor's genesis must remain open.

Differential Diagnosis

It is our impression that the tubular, acinar, follicular, or, at least, gland-like element of the tumor is composed of *epithelial* cells. The variation from low-columnar to flattened cuboidal cells growing with an epithelial cohesiveness is best illustrated in regions showing cord-like growth (Figs. 2 and 5). The tendency of these cells to develop vacuoles is another epithelial characteristic (Figs. 5 and 6).

Those authors who have considered the tumor endothelial in origin (Rigano-Irrera,⁴ Charache,⁵ Malisoff and Helpern,⁶ Mercandier and Thomas ⁷) appear to have accepted the flattened cuboidal appearance of the tumor where large spaces are formed as the cell type (Fig. 8). An examination of their photomicrographs and of our material shows an essential difference cytologically between these cells and endothelium elsewhere, even in angiomas. In the latter tumor group, lining endothelial cells preserve the typical endothelial, central nuclear bulge in a spindle-shaped cell which has sharply tapering ends. In our series of genital tract tumors the whole cell is flattened and never spindly.

Evans ⁸ proposed the reasonable hypothesis that these tumors are mesothelial in origin, because of their location on or near mesothelial surfaces either in the epididymis, tunics of the testicle or uterine serosa. Aside from the historic errors of oncologists in postulating mesothelial

origin to neoplasms of obscure origin, this hypothesis fails to explain the marked tendency towards vacuole formation and the gland-like special arrangement of cells. These properties are described neither for normal mesothelium nor for the more commonly accepted mesotheliomas, such as those of the pleura. Occasionally, one sees prominent mesothelium in various stages of inflammation, as in pleuritis, pericarditis and peritonitis. By using the comparison microscope it is clearly evident that the cells of this tumor are markedly different from even swollen mesothelial cells. In organizing or organized inflammations in such sites (pericardium, pleura or peritoneum) one may see pinched-off mesothelial cell clusters, still viable in a fibrous background. These, too, show marked cytologic differences when compared side by side with these tumor cells, and certainly show no tendency towards vacuolization. Finally, while it seemed obvious in Evans' series that there was an intimate serosal connection in his 4 cases,8 no such clear-cut uniformity of continuity is present in our series of 15 cases.

The stromal background is variable, both in different areas of the same tumor and in different cases. The collagenous stroma may be of variable density. Smooth muscle may be present in isolated strands or in fairly heavy bundles. Our examinations convince us that both strands and bundles represent inclusions of neighboring muscular tissue. Therefore, a compound name such as mixed leiomyoma and lymphangioma (Malisoff and Helpern, and Halpert) does not appear justified. Similar objections may be raised against the designation adenomyoma (Sakaguchi and Falconer).

In a discussion of pseudo-tumors of the epididymis, Mark ¹² described a similar tumor, judging by the text descriptions and the accompanying photomicrograph. He postulated a chronic inflammatory lesion as the basis for the histologic picture. While it is true that a diffuse lymphocytic infiltration and even nodular lymphocytic accumulations are present in these tumors, there is no other evidence of inflammation; nor do any of the known chronic inflammatory conditions of these genital structures result in such tissue alterations.

Thompson ² and Hinman and Gibson ¹ reported similar, if not identical, tumors and described them as adenocarcinomas of a low grade of malignancy. In our series there is no evidence of invasion of the regional tissue even in our cases of 10 years' duration. Follow-up information is available in only 1 of our cases (A.M.M. Accession 76268) where in 4½ years following removal there was no evidence of either recurrence or spread.

On the basis of our analysis it appears to us that the primary unit of the tumor is epithelial in nature and that it tends to form gland-like spaces and, therefore, deserves the name adenoma, as is suggested by Gordon-Taylor and Ommaney-Davis, 13 and by Blumer and Edwards. 14 However, the genesis of the tumor is obscure. We cannot be certain that these elements arise from a pre-existing glandular structure. In the present state of our knowledge it is proposed that the designation adenomatoid be given to this tumor type. The proposed name has the advantage of being morphologically correct and genetically neutral.

Natural History of This Tumor Group

The first impression one receives in examining these tumors microscopically is frequently that of disorderly epithelial proliferation. In our series a diagnosis of malignancy was frequently made by the primary examiner. Clinically and pathologically the evidence favors benignancy. Where long periods intervened between discovery of the tumor and operation, there was no histologic difference in the tumor type as compared to those removed soon after discovery. One does not expect this sort of constancy in a malignant tumor. When first found at autopsy, or incidentally at operation, the tumors are fairly large without evidence of local invasion or distant metastases. Mitotic figures are very rare in all cases. The question as to whether these tumors can become invasive and metastasize in time cannot be answered from the data available. Most of the tumors grew slowly, according to the clinical data. The clinical description of a period of rapid growth immediately antecedent to surgical removal does not appear to be borne out by microscopic examination of the tissue. There is neither evidence of mitotic cellular proliferation nor of marked regional tissue compression such as would be the case in rapidly expanding tumors. As has been suggested, some of the clinical impressions of increased size may be due to partial compression or obstruction of venous or lymphatic return from the regional tissues, producing an increase of size in the area involved. A history of trauma and subsequent growth was present in 2 cases. The relationship to trauma is obscure and there is no evidence in regional tissues that trauma may have played a rôle. One does not find areas of fat necrosis or organized hemorrhage, for example. Furthermore, it should be noted that identical tumors were found in 2 instances in this series in the uterine tube, again without microscopic evidence of trauma.

Biologic Activity of the Tumor Group

In 1 of our cases the Aschheim-Zondek test was performed prior to surgical removal and was reported as negative. In the case reported by Malisoff and Helpern ⁶ a positive test was recorded, but in that case discussion brought out that it may have been a false positive test.

SUMMARY

Fifteen cases of an apparently benign tumor of the genital tract in males and females are reported and the pertinent pathologic and clinical findings summarized. An argument has been presented for designating these neoplasms as adenomatoid tumors. Adenomatoid tumors of the genital tract have a well defined glandular pattern, as a rule, arranged spatially in many planes with considerable variation in size of lumina and cell structure. They may suggest malignant tumors on primary microscopic examination, particularly by the frozen section method. Both in our series and in reported cases there has been no evidence of malignancy if mitotic activity, local tissue invasion, and metastasis are considered. The clinical data also suggest the benign nature of the tumor group. The origin of this tumor is obscure.

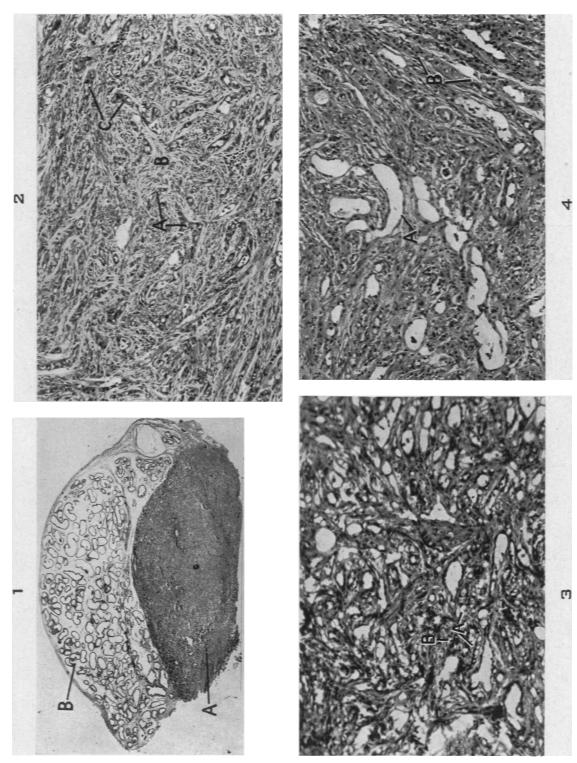
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DESCRIPTION OF PLATES

PLATE 12

- Fig. 1. Acc. 81346, Neg. no. 74712. Low-power view of the relationship of the tumor (A) to the epididymis (B). \times 5.
- FIG. 2. Acc. 84648, Neg. no. 74708. There is a predominantly solid growth in cords (A) in a dense fibrous stroma (B). Vacuolated cells are seen at C. × 118.
- Fig. 3. Acc. 84648, Neg. no. 74709. The tumor pattern is microfollicular. Vacuolated cells are seen at A; scattered lymphocytes at B. × 118.
- Fig. 4. Acc. 84615, Neg. no. 74714. The pattern is chiefly macrofollicular (A). Solid cords of cells (B) are present also. \times 118.

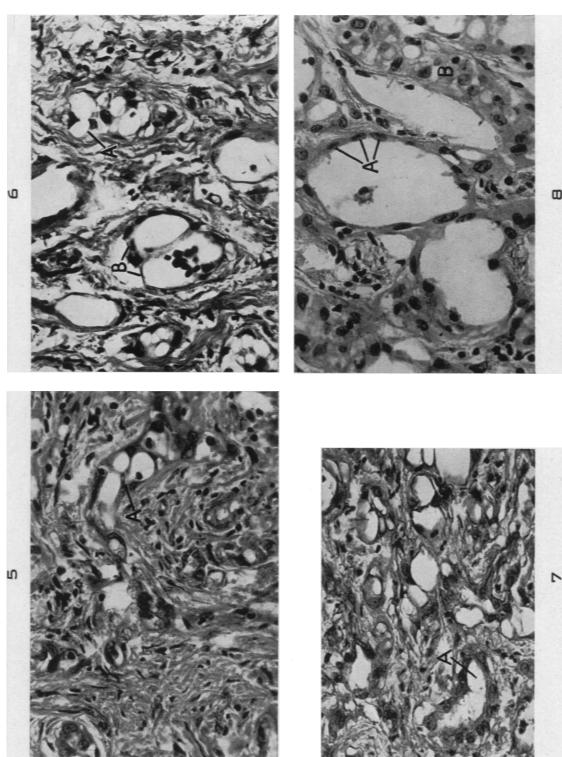


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PLATE 13

- Fig. 5. Acc. 84648, Neg. no. 74710. The vacuolated type of cell (A), of moderate size. \times 395.
- Fig. 6. Acc. 76268, Neg. no. 74705. Larger cell vacuoles producing signet rings (A), and very large, multinucleated vacuolated cells (B). \times 395.
- Fig. 7. Acc. 81346, Neg. no. 74711. A gland-like space (A) with cytoplasmic spurs along the free cell border. \times 395.
- Fig. 8. Acc. 84615, Neg. no. 74715. The cell type seen in the macrofollicular pattern. The whole cell is flattened, but is still cuboidal, and not spindly (A). There are vacuolated cell cords between the macrofollicular structures (B). × 395.



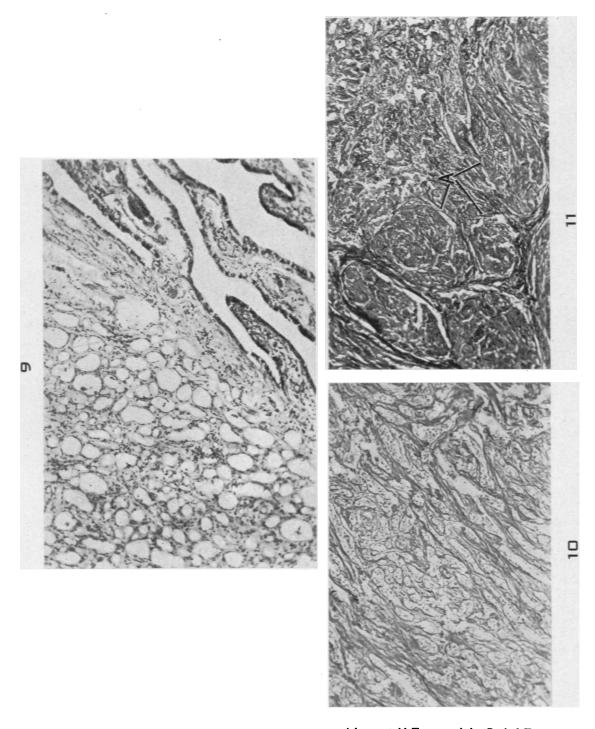
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PLATE 14

- Fig. 9. Acc. 91983, A-36-1427, Neg. no. 77134. The neoplasm present in one of the two cases of involvement of a uterine tube. \times 74.
- Fig. 10. Acc. 84615, Neg. no. 77131. The reticulum meshwork has a fine to coarse perifollicular arrangement. \times 74.
- Fig. 11. Acc. 84615, Neg. no. 77130. Smooth muscle bundle inclusions in this instance have an arrangement (A) which is almost myomatous. \times 74.



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